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(71) Applicant (*for all designated States except US*): ALKERMES, INCORPORATED [US/US]; 64 Sidney Street, Cambridge, MA 02139 (US).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): HARBESON, Scott, L. [US/US]; Apartment 5, 203 Pemberton Street, Cambridge, MA 02140 (US). STRAUB, Julie, Ann [US/US]; 16 Plato Terrace, Winchester, MA 01890 (US).

(74) Agents: BROOK, David, E. et al.; Hamilton, Brook, Smith & Reynolds, P.C., Two Militia Drive, Lexington, MA 02173 (US).

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(54) Title: OPTICALLY PURE CALPAIN INHIBITOR COMPOUNDS

(57) Abstract

Optically pure α-ketoamide compounds, and use therefor in treating neurodegenerative pathologies having enhanced Calpain activity, are disclosed. These compounds comprise optically pure α-ketoamides, and physiologically acceptable salts thereof, wherein the α-ketoamide contains an amino acid isomer which has an L-configuration about the chiral center which is structurally located in the α position to the ketone of the α-ketoamide, and wherein the amide functionality of the α-ketoamide portion of the compound's molecule is derived from an amine of an amino acid or an amine substituted with a sulfone functionality. The method of treating a human neurodegenerative pathology, having enhanced Calpain activity, with a Calpain inhibitor composition while reducing undesirable inhibition of other cysteine proteases andother side effects associated with the racemic Calpain inhibitor composition includes administering an optically pure L-isomer of an α-ketoamide compound, wherein the L-isomer is substantially free of its D-isomer. The method of forming an optically pure L-α-ketoamide includes mixing an L-β-amino-α-hydroxyamide in a solution containing a free radical catalyst and then mixing an oxydizing agent into said solution under conditions sufficient to form said optically pure L-α-ketoamide.

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CLAIMS

1. A compound represented by the formula:
$M\text{-}AA^1_x\text{-}AA^2\text{-}NHCH(R^1)CO\text{-}CO\text{-}NH\text{-}R^2\text{-}SO_2\text{-}R^3$
and physiologically acceptable salts thereof, wherein

M is H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, R^7-NH-CO-, R^7_2N-CO-, R^7-NH-CS-, R^7_2N-CS-, R^7-NH-SO_2-, R^7_2N-SO_2-, R^7-CO-, R^7-CS-, R^7-SO_2-, R^7-O-CO-, R^7-O-CS-, R^8N-CO-, R^8N-CS- or R^8N-SO_2-;

R^7 is a C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluoroalkyl, phenyl substituted n times with K, naphthyl substituted n times with K, C_{1-10} alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, or C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

n is 0, 1, 2 or 3;

J is a halogen, hydroxyl, carboxy, cyano, amino, nitro, C_{1-10} alkyoxy, C_{1-10} alkamino, C_{2-12} dialkamino, C_{1-10} alkoxy-CO- group, C_{1-10} alkoxy-NH- group, C_{1-10} alkyl-S- group, or C_{1-10} alkyl-SO_2- group;

K is a halogen, hydroxyl, carboxy, cyano, amino, nitro, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkamino, C_{2-12} dialkamine, C_{1-10} alkoxy-CO- group, C_{1-10} acyl, C_{1-10} alkyloxy group, C_{1-10} alkyl-S- group or C_{1-10} alkyl-SO_2- group;

R^8N is a C_{3-6} saturated or unsaturated heterocycle containing at least one nitrogen atom. Said heterocycle can contain Q additional heteroatoms selected from the group consisting of nitrogen, oxygen, sulfur and combinations thereof.

Further, said heterocycle can be substituted with one or more substituents selected from the group consisting of a hydroxyl, halogen, alkyl, cycloalkyl, aryl, alkoxy, alkoxycarbonyl, alkylthio and amino.

Q is 0, 1 or 2;

AA^1 is an amino acid residue of a side chain blocked or unblocked amino acid, with the L configuration, D configuration or no chirality at the α-carbon, wherein said amino acid is selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfone, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, ß-alanine, norleucine, norvaline, α-aminobutyric acid, ϵ-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline-2-carboxylic acid, 2-azetidine-carboxylic acid, pipecolinic acid, O-methylserine, O-ethyl-serine, S-methylcysteine, S-ethylcysteine, S-benzyl-cysteine, S-methylcysteine sulfone, S-ethylcysteine sulfone, S-benzyl-cysteine sulfone, cyclohexylalinine, homophenylalanine, p-chloro-phenylalanine, p-nitro-phenylalanine, p-amino-phenylalanine, 4-methoxy-phenylalanine, thienylalanine, pyridylalanine, NH_2-$CH(CH_2CH(CH_2CH_3)_2)$-COOH, α-aminoheptanoic acid, NH_2-CH(CH_2-1-naphthyl)-COOH, NH_2-CH(CH_2-2-naphthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl-butyl)-COOH,

trifluoroleucine or hexafluoroleucine;

X is 0, 1, 2 or 3;

AA^2 is an amino acid residue of a side chain blocked or unblocked amino acid, with the L or D configuration at the α-carbon, wherein said amino acid residue imparts calpain-specificity to calpain inhibitor molecules;

$NHCH(R^1)CO$ is a side chain blocked or unblocked amino acid with the L configuration and wherein R^1 is a branched or unbranched C_{1-8} alkyl, cycloalkyl of fluoroalkyl;

R^2 is a branched or unbranched, saturated or unsaturated constituent selected from the group consisting of C_{1-20} alkyl, C_{1-20} cycloalkyl, C_{1-20} alkyl with an attached phenyl group which is substituted n times with K, and C_{1-20} cycloalkyl with an attached phenyl group which is substituted n times with K, and wherein said constituent can be substituted one or more times with Z;

Z is a hydroxyl, carboxy, alkoxy, alkoxymethoxy, alkanoate, alky; carbamyl, $-O-CH_2-SO_2-CH_3$ group, $-OCH_2CH_2-O-CH_2CH_2-OH$ group, or $-OCH_2CH_2-O-CH_2CH_2-OCH_3$ group; and

R^3 is R^2, -OH, $-OR^2$, NH_2, NHR^2 or NR^2R^2.

2. A compound represented by the formula:

$M-AA^1{}_x-AA^2-AA^3-CO-NH-R^2-SO_2-R^3$

and physiologically acceptable salts thereof, wherein

M is H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, $R^7-NH-CO-$, $R^7{}_2N-CO-$, $R^7-NH-CS-$, $R^7{}_2N-CS-$, $R^7-NH-SO_2-$, $R^7{}_2N-SO_2-$,

R^7-CO-, R^7-CS-, R^7-SO_2-, R^7-O-CO-, R^7-O-CS-, R^8N-CO-, R^8N-CS- or R^8N-SO_2-;

R^7 is a C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluoroalkyl, phenyl substituted n times with K, naphthyl substituted n times with K, C_{1-10} alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, or C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

n is 0, 1, 2 or 3;

J is a halogen, hydroxyl, carboxy, cyano, amino, nitro, C_{1-10} alkyoxy, C_{1-10} alkamino, C_{2-12} dialkamino, C_{1-10} alkoxy-CO- group, C_{1-10} alkoxy-NH- group, C_{1-10} alkyl-S- group, or C_{1-10} alkyl-SO_2- group;

K is a halogen, hydroxyl, carboxy, cyano, amino, nitro, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkamino, C_{2-12} dialkamine, C_{1-10} alkoxy-CO- group, C_{1-10} acyl, C_{1-10} alkyloxy group, C_{1-10} alkyl-S- group or C_{1-10} alkyl-SO_2- group;

R^8N is a C_{3-6} saturated or unsaturated heterocycle containing at least one nitrogen atom. Said heterocycle can contain Q additional heteroatoms selected from the group consisting of nitrogen, oxygen, sulfur and combinations thereof. Further, said heterocycle can be substituted with one or more substituents selected from the group consisting of a hydroxyl, halogen, alkyl, cycloalkyl, aryl, alkoxy, alkoxycarbonyl, alkylthio and amino.

Q is 0, 1 or 2;

AA^1 is an amino acid residue of a side chain blocked or unblocked amino acid, with the L configuration, D configuration or no chirality at the α-carbon, wherein said amino acid is selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfone, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, ß-alanine, norleucine, norvaline, α-aminobutyric acid, ϵ-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline-2-carboxylic acid, 2-azetidine-carboxylic acid, pipecolinic acid, O-methylserine, O-ethyl-serine, S-methylcysteine, S-ethylcysteine, S-benzyl-cysteine, S-methylcysteine sulfone, S-ethylcysteine sulfone, S-benzyl-cysteine sulfone, cyclohexylalinine, homophenylalanine, p-chloro-phenylalanine, p-nitro-phenylalanine, p-amino-phenylalanine, 4-methoxy-phenylalanine, thienylalanine, pyridylalanine, NH_2-$CH(CH_2CH(CH_2CH_3)_2)$-COOH, α-aminoheptanoic acid, NH_2-CH(CH_2-1-naphthyl)-COOH, NH_2-CH(CH_2-2-naphthyl)-COOH, NH_2-CH(CH_2-cyclohexyl)-COOH, NH_2-CH(CH_2-cyclopentyl)-COOH, NH_2-CH(CH_2-cyclobutyl)-COOH, NH_2-CH(CH_2-cyclopropyl-butyl)-COOH, trifluoroleucine or hexafluoroleucine;

X is 0, 1, 2 or 3;

AA^2 is an amino acid residue of a side chain blocked or unblocked amino acid, with the L or D

configuration at the α-carbon, wherein said amino acid residue imparts calpain-specificity to calpain inhibitor molecules;

AA^3 is an amino acid residue of a side chain blocked or unblocked amino acid, with the L configuration at the α-carbon, wherein said amino acid is selected from the group consisting of alanine, α-aminobutyric acid, norvaline, valine, norleucine, leucine, phenylalanine, tyrosine, cyclohexylalanine, homophenylalanine, p-chloro-phenylalanine, p-nitro-phenylalanine, p-amino-phenylalanine, thionylalanine, lysine, ornithine, aspartic acid, glutamic acid, serine, threonine, pyridylalanine or 4-methoxy-phenylalanine;

R^2 is a branched or unbranched, saturated or unsaturated constituent selected from the group consisting of C_{1-20} alkyl, C_{1-20} cycloalkyl, C_{1-20} alkyl with an attached phenyl group which is substituted n times with K, and C_{1-20} cycloalkyl with an attached phenyl group which is substituted n times with K, and wherein said constituent can be substituted one or more times with Z;

Z is a hydroxyl, carboxy, alkoxy, alkoxymethoxy, alkanoate, alky; carbamyl, $-O-CH_2-SO_2-CH_3$ group, $-OCH_2CH_2-O-CH_2CH_2-OH$ group, or $-OCH_2CH_2-O-CH_2CH_2-OCH_3$ group; and

R^3 is R^2, -OH, $-OR^2$, NH_2, NHR^2 or NR^2R^2.

3. A compound represented by the formula:

$$M-AA^1{}_x-AA^2-NHCH(R^1)CO-CO-AA^4-OR^4$$

and physiologically acceptable salts thereof, wherein

M is H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, $R^7-NH-CO-$, $R^7{}_2N-CO-$, $R^7-NH-CS-$, $R^7{}_2N-CS-$, $R^7-NH-SO_2-$, $R^7{}_2N-SO_2-$,

R^7-CO-, R^7-CS-, R^7-SO_2-, R^7-O-CO-, R^7-O-CS-, R^8N-CO-, R^8N-CS- or R^8N-SO_2-;

R^7 is a C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluoroalkyl, phenyl substituted n times with K, naphthyl substituted n times with K, C_{1-10} alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, or C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

n is 0, 1, 2 or 3;

J is a halogen, hydroxyl, carboxy, cyano, amino, nitro, C_{1-10} alkyoxy, C_{1-10} alkamino, C_{2-12} dialkamino, C_{1-10} alkoxy-CO- group, C_{1-10} alkoxy-NH- group, C_{1-10} alkyl-S- group, or C_{1-10} alkyl-SO_2- group;

K is a halogen, hydroxyl, carboxy, cyano, amino, nitro, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkamino, C_{2-12} dialkamine, C_{1-10} alkoxy-CO- group, C_{1-10} acyl, C_{1-10} alkyloxy group, C_{1-10} alkyl-S- group or C_{1-10} alkyl-SO_2- group;

R^8N is a C_{3-6} saturated or unsaturated heterocycle containing at least one nitrogen atom. Said heterocycle can contain Q additional heteroatoms selected from the group consisting of nitrogen, oxygen, sulfur and combinations thereof. Further, said heterocycle can be substituted with one or more substituents selected from the group consisting of a hydroxyl, halogen, alkyl, cycloalkyl, aryl, alkoxy, alkoxycarbonyl, alkylthio and amino.

Q is 0, 1 or 2;

AA^1 is an amino acid residue of a side chain blocked or unblocked amino acid, with the L configuration, D configuration or no chirality at the α-carbon, wherein said amino acid is selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfone, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, ß-alanine, norleucine, norvaline, α-aminobutyric acid, ϵ-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline-2-carboxylic acid, 2-azetidine-carboxylic acid, pipecolinic acid, O-methylserine, O-ethyl-serine, S-methylcysteine, S-ethylcysteine, S-benzyl-cysteine, S-methylcysteine sulfone, S-ethylcysteine sulfone, S-benzyl-cysteine sulfone, cyclohexylalinine, homophenylalanine, p-chloro-phenylalanine, p-nitro-phenylalanine, p-amino-phenylalanine, 4-methoxy-phenylalanine, thienylalanine, pyridylalanine, NH_2-$CH(CH_2CH(CH_2CH_3)_2)$-COOH, α-aminoheptanoic acid, NH_2-$CH(CH_2$-1-naphthyl)-COOH, NH_2-$CH(CH_2$-2-naphthyl)-COOH, NH_2-$CH(CH_2$-cyclohexyl)-COOH, NH_2-$CH(CH_2$-cyclopentyl)-COOH, NH_2-$CH(CH_2$-cyclobutyl)-COOH, NH_2-$CH(CH_2$-cyclopropyl-butyl)-COOH, trifluoroleucine or hexafluoroleucine;

X is 0, 1, 2 or 3;

AA^2 is an amino acid residue of a side chain blocked or unblocked amino acid, with the L or D configuration at the α-carbon, wherein said amino acid residue imparts calpain-specificity

to calpain inhibitor molecules;

NHCH(R^1)CO is a side chain blocked or unblocked amino acid with the L configuration and wherein R^1 is a branched or unbranched C_{1-8} alkyl, cycloalkyl of fluoroalkyl;

AA^4 is an amino acid residue of a side chain blocked or unblocked amino acid, with the L configuration, D configuration or no chirality at the α-carbon, wherein said amino acid is selected from the group consisting of glycine, ß-alanine, alanine, α-aminobutyric acid, norvaline, valine, norleucine, leucine, phenylalanine, tyrosine, cyclohexylalanine, homophenylalanine, p-chloro-phenylalanine, p-nitro-phenylalanine, p-amino-phenylalanine, thionylalanine, lysine, ornithine, aspartic acid, glutamic acid, serine, threonine, pyridylalanine or 4-methoxy-phenylalanine; and

R^4 is H, C_{1-20} alkyl, aryl, C_{1-20} alkyl with an attached phenyl group, or C_{1-20} alkyl with an attached phenyl group substituted with K.

4. A compound represented by the formula:

$M\text{-}AA^1_x\text{-}AA^2\text{-}AA^3\text{-}CO\text{-}AA^4\text{-}OR^4$

and physiologically acceptable salts thereof, wherein

M is H, NH_2-CO-, NH_2-CS-, NH_2-SO_2-, R^7-NH-CO-, $R^7{}_2$N-CO-, R^7-NH-CS-, $R^7{}_2$N-CS-, R^7-NH-SO_2-, $R^7{}_2$N-SO_2-, R^7-CO-, R^7-CS-, R^7-SO_2-, R^7-O-CO-, R^7-O-CS-, R^8N-CO-, R^8N-CS- or R^8N-SO_2-;

R^7 is a C_{1-10} alkyl, C_{1-10} fluoroalkyl, C_{1-10} alkyl substituted with J, C_{1-10} fluoroalkyl substituted with J, 1-admantyl, 9-fluoroalkyl, phenyl substituted n times with K, naphthyl substituted n times with K, C_{1-10} alkyl with an attached phenyl group substituted with K, C_{1-10} alkyl with

two attached phenyl groups substituted with K, C_{1-10} alkyl with an attached phenoxy group, or C_{1-10} alkyl with an attached phenoxy group substituted with K on the phenoxy group;

n is 0, 1, 2 or 3;

J is a halogen, hydroxyl, carboxy, cyano, amino, nitro, C_{1-10} alkyoxy, C_{1-10} alkamino, C_{2-12} dialkamino, C_{1-10} alkoxy-CO- group, C_{1-10} alkoxy-NH- group, C_{1-10} alkyl-S- group, or C_{1-10} alkyl-SO_2- group;

K is a halogen, hydroxyl, carboxy, cyano, amino, nitro, C_{1-10} alkyl, C_{1-10} perfluoroalkyl, C_{1-10} alkamino, C_{2-12} dialkamine, C_{1-10} alkoxy-CO- group, C_{1-10} acyl, C_{1-10} alkyloxy group, C_{1-10} alkyl-S- group or C_{1-10} alkyl-SO_2- group;

R^8N is a C_{3-6} saturated or unsaturated heterocycle containing at least one nitrogen atom. Said heterocycle can contain Q additional heteroatoms selected from the group consisting of nitrogen, oxygen, sulfur and combinations thereof. Further, said heterocycle can be substituted with one or more substituents selected from the group consisting of a hydroxyl, halogen, alkyl, cycloalkyl, aryl, alkoxy, alkoxycarbonyl, alkylthio and amino;

Q is 0, 1 or 2;

AA^1 is an amino acid residue of a side chain blocked or unblocked amino acid, with the L configuration, D configuration or no chirality at the α-carbon, wherein said amino acid is selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfone, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine,

asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, ß-alanine, norleucine, norvaline, α-aminobutyric acid, ϵ-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline-2-carboxylic acid, 2-azetidine-carboxylic acid, pipecolinic acid, O-methylserine, O-ethyl-serine, S-methylcysteine, S-ethylcysteine, S-benzyl-cysteine, S-methylcysteine sulfone, S-ethylcysteine sulfone, S-benzyl-cysteine sulfone, cyclohexylalinine, homophenylalanine, p-chloro-phenylalanine, p-nitro-phenylalanine, p-amino-phenylalanine, 4-methoxy-phenylalanine, thienylalanine, pyridylalanine, NH_2-$CH(CH_2CH(CH_2CH_3)_2)$-COOH, α-aminoheptanoic acid, NH_2-$CH(CH_2$-1-naphthyl)-COOH, NH_2-$CH(CH_2$-2-naphthyl)-COOH, NH_2-$CH(CH_2$-cyclohexyl)-COOH, NH_2-$CH(CH_2$-cyclopentyl)-COOH, NH_2-$CH(CH_2$-cyclobutyl)-COOH, NH_2-$CH(CH_2$-cyclopropyl-butyl)-COOH, trifluoroleucine or hexafluoroleucine;

X is 0, 1, 2 or 3;

AA^2 is an amino acid residue of a side chain blocked or unblocked amino acid, with the L or D configuration at the α-carbon, wherein said amino acid residue imparts calpain-specificity to calpain inhibitor molecules;

AA^3 is an amino acid residue of a side chain blocked or unblocked amino acid, with the L configuration at the α-carbon, wherein said amino acid is selected from the group consisting of alanine, α-aminobutyric acid, norvaline, valine, norleucine, leucine, phenylalanine, tyrosine, cyclohexylalanine, homophenylalanine, p-chloro-phenylalanine, p-nitro-phenylalanine,

p-amino-phenylalanine, thionylalanine, lysine, ornithine, aspartic acid, glutamic acid, serine, threonine, pyridylalanine or 4-methoxy-phenylalanine;

AA^4 is an amino acid residue of a side chain blocked or unblocked amino acid, with the L configuration, D configuration or no chirality at the α-carbon, wherein said amino acid is selected from the group consisting of glycine, ß-alanine, alanine, α-aminobutyric acid, norvaline, valine, norleucine, leucine, phenylalanine, tyrosine, cyclohexylalanine, homophenylalanine, p-chloro-phenylalanine, p-nitro-phenylalanine, p-amino-phenylalanine, thionylalanine, lysine, ornithine, aspartic acid, glutamic acid, serine, threonine, pyridylalanine or 4-methoxy-phenylalanine; and

R^4 is H, C_{1-20} alkyl, aryl, C_{1-20} alkyl with an attached phenyl group, or C_{1-20} alkyl with an attached phenyl group substituted with K.

5. A Calpain inhibitor composition, comprising an optically pure L-isomer of an α-ketoamide compound, said L-isomer being substantially free of its D-isomer, for use as a medicament in treating a human neurodegenerative pathology having enhanced Calpain activity.

6. A method of treating a human neurodegenerative pathology, having enhanced Calpain activity, with a Calpain inhibitor composition, while reducing inhibition of other catalytic proteases and other side effects associated with the racemic calpain inhibitor composition and other side effects, comprising administering to the individual a quantity